Appendix: Sensitivity analyses.

We performed several sensitivity analyses.

To address potential confounding, we: (1) excluded individuals presenting late to care (initiating cART at CD4 cell count≤200 cells/µl); (2) excluded intravenous drug users and those with an unknown mode of transmission; (3) restricted the analysis to individuals who achieved confirmed virologic suppression within 8 months of cART initiation; (4) additionally adjusted for the number of months since the last clinic visit in cohorts for which a clinic visit could be recorded without a CD4 cell count or HIV-RNA measurement being recorded; and (5) additionally adjusted for months since the first treatment switch among individuals who switched treatment after baseline. We defined a treatment switch as a change of treatment regimen after baseline to a new regimen, as described previously.[1]

To address potential selection bias, we adjusted for censoring due to death for immunologic and virologic outcomes using inverse probability weighting.

To determine whether our findings differed across calendar time or cohort, we: (1) restricted the analysis to those initiating cART in 2004 or later; and (2) excluded large individual cohorts (VACS, FHDH, and CNICS) from the analysis.

We also: (1) explored alternative definitions of virologic suppression (e.g. HIV-RNA≤50 copies/ml); (2) restricted the analysis to individuals with baseline CD4 cell counts above a given value (200 and 500 cells/µl) to decrease the number of individuals following more than one monitoring strategy over follow-up; and (3) included individuals with AIDS at baseline.

Appendix Table 1. Contributions to the weights at different time points for strategies with monitoring at the end of the grace period (partially stabilized) and strategies with uniform monitoring, HIV-CAUSAL and CNICS Collaborations 2000-2015.

Time point	Monitor	Type of weights			
		Nonstabilized	Partially stabilized*	Uniform monitoring**	Product of partially stabilized and uniform monitoring (used in analysis)
Before grace period j<0	None	$\frac{1}{p\_d\_0}$	$\frac{p\_w\_n}{p\_d\_0}$	$\frac{1}{p\_d\_0}$	$\frac{p\_w\_n}{p\_d\_0}$
During grace period 0≤j<m	Double	$\frac{1}{1-p\_d\_1}$	$\frac{p\_w\_n}{1-p\_d\_1}$	$\frac{1/(m+1-j)}{p\_d\_2}$	$\frac{p\_w\_n * 1/(m+1-j)}{p\_d\_2}$
	None	$\frac{1}{1-p\_d\_1}$	$\frac{p\_w\_n}{1-p\_d\_1}$	$\frac{1-[\frac{1}{m+1-j}]}{1-p\_d\_2}$	$\frac{p\_w\_n * (1-\left[\frac{1}{m+1-j}\right])}{1-p\_d\_2}$
End of grace period j=m	Double	$\frac{1}{p\_d\_2}$	$\frac{p\_w\_n}{p\_d\_2}$	$\frac{1/(m+1-j)}{p\_d\_2}$	$\frac{p\_w\_n * 1/(m+1-j)}{p\_d\_2}$

*Corresponds to strategies where monitoring occurs at the end of the grace period

**Corresponds to strategies where monitoring occurs with uniform probability during the grace period

m, length of grace period

j, position in grace period (month)

p_d_2, conditional probability of having CD4 and RNA monitored

p_d_1, conditional probability of having one measurement

p_d_0, conditional probability of not being monitored

p_w_n, conditional probability of not being censored, estimated from a model fit in the expanded population after censoring

Appendix Table 2. Association of prognostic factors with CD4 cell count monitoring, CNICS and HIV-CAUSAL Collaboration 2000-2015

Baseline characteristic		Odds ratio (95% CI)*
CD4 cell count (cell/µl)		
	<200	1 (reference)
	200 to < 350	1.11 (1.09, 1.12)
	350 to < 500	1.19 (1.18, 1.21)
	≥500	1.23 (1.21, 1.24)
Sex		
	Male	1 (reference)
	Female	1.05 (1.04, 1.06)
Race		
	White	1 (reference)
	Black	0.92 (0.91, 0.93)
	Other/unknown	0.98 (0.97, 0.99)
Age (years)		
	<35	1 (reference)
	35-50	1.05 (1.04, 1.06)
	>50	1.14 (1.13, 1.15)
Origin		
	North America or Western Europe	1 (reference)
	Sub-Saharan Africa	1.01 (0.99, 1.02)
	Other	0.93 (0.92, 0.95)
	Unknown	0.98 (0.98, 0.99)
Acquisition Group		
	Heterosexual	1 (reference)
	Homo/bisexual	1.00 (0.99, 1.01)
	Injection Drug User	0.96 (0.95, 0.98)
	Other/Unknown	1.08 (1.07, 1.10)
Calendar Year		
	2000-2002	1 (reference)
	2003-2005	0.93 (0.92, 0.94)
	2006-2008	0.84 (0.83, 0.85)
	≥2009	0.69 (0.69, 0.70)
Months to Suppression		
	2-4	1 (reference)
	5-8	0.93 (0.92, 0.94)
	9-12	0.87 (0.86, 0.88)
Years since HIV diagnosis		
	<1	1 (reference)
	1- < 5	0.98 (0.97, 0.99)
	5 or more or unknown	1.03 (1.02, 1.03)
Time-varying characteristic		
Most recent CD4 cell count (cell/µl)		
	<200	1 (reference)
	200 to < 350	0.83 (0.81, 0.84)
	350 to < 500	0.70 (0.69, 0.71)
	≥500	0.59 (0.58, 0.60)

Most recent HIV-RNA (copies/ml)	
≤200	1 (reference)
201-999	1.25 (1.22, 1.28)
1,000-9,999	1.13 (1.10, 1.16)
≥10,000	1.14 (1.12, 1.16)
Diagnosis of AIDS-defining illness	
no	1 (reference)
yes	0.99 (0.97, 1.02)
Average proportion of months with a CD4 measurement	
<1/9	1 (reference)
1/9 to < 1/6	0.81 (0.78, 0.84)
1/6 to < 1/3	1.30 (1.26, 1.34)
≥1/3	2.09 (2.02, 2.16)
Time since last CD4 cell count at previous month	
0 or 1 months	1 (reference)
2 or 3 months	2.68 (2.63, 2.73)
4 or more months	2.16 (2.12, 2.19)
Average proportion of months with an RNA measurement	
<1/9	1 (reference)
1/9 to < 1/6	1.76 (1.67, 1.86)
1/6 to < 1/3	2.25 (2.13, 2.37)
≥1/3	3.44 (3.26, 3.62)
Time since last RNA measurement at previous month	
0 or 1 months	1 (reference)
2 or 3 months	2.96 (2.91, 3.01)
4 or more months	3.73 (3.66, 3.80)

*The odds ratios were obtained by fitting a pooled logistic regression model in the original, unexpanded population for CD4 monitoring (yes/no) conditional on each of the listed baseline and time-varying covariates.

An analysis of prognostic factors and RNA monitoring produced similar results.

Appendix Table 3. Treatment switching by monitoring strategy, HIV-CAUSAL and CNICS Collaborations 2000-2015.

Monitoring strategy	Outcomes, cases	Person-months	Unadjusted hazard ratio (95% CI)	Baseline-adjusted hazard ratio* (95% CI)	Fully-adjusted hazard ratios** (95% CI)
"Threshold 200"	1,615	200,013	0.95 (0.93, 0.98)	0.94 (0.92, 0.97)	0.96 (0.93, 0.99)
"Threshold 350"	1,961	286,282	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)	0.99 (0.96, 1.01)
"Threshold 500"	2,408	428,523	1.00 (reference)	1.00 (reference)	1.00 (reference)

*From unweighted model including the baseline covariates sex, age, race, geographic origin, acquisition group, CD4 cell count, HIV-RNA, calendar year, years since HIV diagnosis, cohort, and months from cART initiation to virologic suppression.

**From inverse probability weighted model. IP weights were a function of the baseline covariates (above) and the time-varying covariates CD4 cell count, HIV-RNA, diagnosis of an AIDS-defining illness, proportion of months of follow-up from baseline to the current observation with a CD4 cell count measurement, and months since the last CD4 cell count measurement.

Appendix Table 4. Hazard ratio of clinical outcomes by monitoring strategy under different levels of adjustment, CNICS and HIV-CAUSAL Collaboration 2000-2015.

Outcome and monitoring strategy	Outcomes, cases	Unadjusted hazard ratio (95% CI)	Baseline-adjusted hazard ratios* (95% CI)	Baseline-adjusted hazard ratio (95% CI) with time-varying covariates in outcome model**
All-cause mortality				
"Threshold 200"	107	1.12 (0.98, 1.28)	1.06 (0.94, 1.21)	0.94 (0.81, 1.10)
"Threshold 350"	157	1.14 (1.05, 1.24)	1.07 (0.98, 1.16)	1.01 (0.91, 1.11)
"Threshold 500"	200	1.00 (reference)	1.00 (reference)	1.00 (reference)
AIDS-defining illness or death				
"Threshold 200"	267	1.12 (1.03, 1.21)	1.05 (0.97, 1.13)	1.00 (0.91, 1.1)
"Threshold 350"	365	1.12 (1.06, 1.18)	1.04 (0.98, 1.09)	1.01 (0.95, 1.08)
"Threshold 500"	459	1.00 (reference)	1.00 (reference)	1.00 (reference)

*Adjusted for the baseline covariates (sex, age, race, geographic origin, acquisition group, CD4 cell count, HIV-RNA, calendar year, years since HIV diagnosis, cohort, and months from cART initiation to virologic suppression).

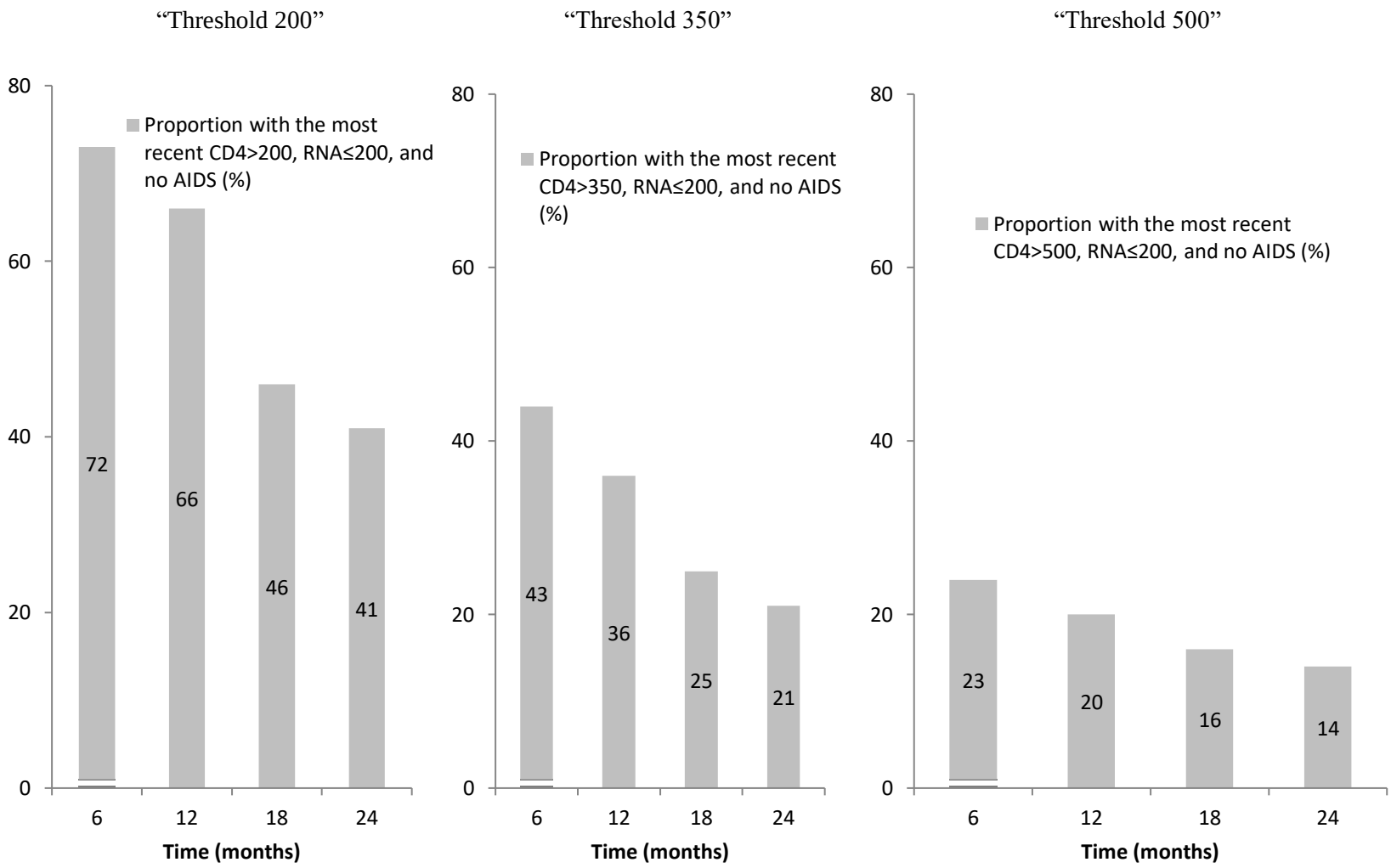
** These hazard ratios are shown for comparison purposes only. They were obtained by including the baseline and time-varying covariates in a model for the outcome, rather than by fitting a weighted regression model for the outcome conditional on the baseline covariates.

Appendix Table 5. Risk of virologic failure by monitoring strategy with alternative definitions of virologic suppression and virologic failure, CNICS and HIV-CAUSAL Collaboration 2000-2015

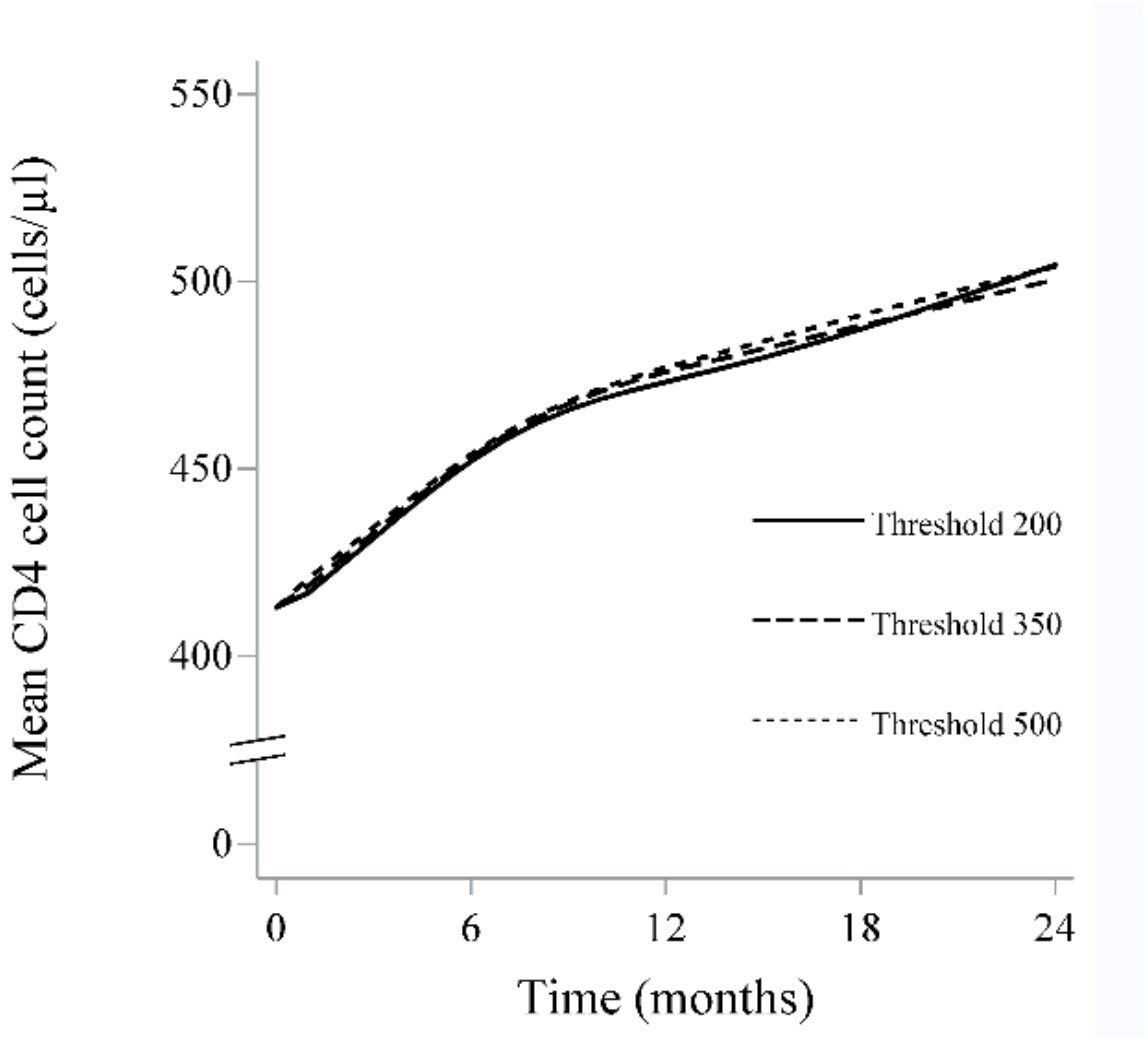
Outcome and monitoring strategy	No. RNA>200 copies / No. RNA>50 copies (no. with RNA measurements at 24 ± 2 months)	Risk ratios* (95% CI)	
		Failure defined as RNA>200 copies/ml	**Failure defined as RNA>50 copies/ml**
Virologic failure at 24 ± 2 months			
Primary analysis (baseline defined as two consecutive HIV-RNA≤200 copies/ml)			
"Threshold 200"	35 / 81 (405)	2.01 (1.17, 3.43)	1.10 (0.73, 1.64)
"Threshold 350"	89 / 278 (1,610)	1.24 (0.89, 1.73)	1.10 (0.89, 1.35)
"Threshold 500"	171 / 570 (3,962)	1.00 (reference)	1.00 (reference)
Baseline defined as two consecutive HIV-RNA≤50 copies/ml			
"Threshold 200"	21 / 36 (293)	1.63 (0.86, 3.09)	1.16 (0.66, 2.01)
"Threshold 350"	57 / 135 (1,293)	1.42 (0.95, 2.14)	1.28 (0.94, 1.74)
"Threshold 500"	121 / 306 (3,261)	1.00 (reference)	1.00 (reference)
Baseline defined as one HIV-RNA≤200 copies/ml			
"Threshold 200"	56 / 116 (507)	1.02 (0.62, 1.69)	1.07 (0.77, 1.49)
"Threshold 350"	146 / 354 (1,886)	0.97 (0.71, 1.32)	0.94 (0.76, 1.16)
"Threshold 500"	273 / 692 (4,392)	1.00 (reference)	1.00 (reference)
Virologic failure at 18 ± 2 months			
Primary analysis (baseline defined as two consecutive HIV-RNA≤200 copies/ml)			
"Threshold 200"	73 / 161 (879)	1.65 (1.16, 2.35)	1.11 (0.87, 1.42)
"Threshold 350"	185 / 459 (2,946)	1.23 (0.96, 1.56)	1.05 (0.91, 1.22)
"Threshold 500"	283 / 864 (6,466)	1.00 (reference)	1.00 (reference)

* Adjusted for the baseline covariates (sex, age, race, geographic origin, acquisition group, CD4 cell count, HIV-RNA, calendar year, years since HIV diagnosis, cohort, and months from cART initiation to virologic suppression). We adjusted for potential selection bias induced by artificial censoring using inverse probability weighting.

Appendix Figure 1. Proportion (%) of individuals within each CD4 cell count, HIV-RNA, and AIDS-defining illness category by monitoring strategy over follow-up, CNICS and HIV-CAUSAL Collaboration 2000-2015. This is also the proportion monitored once every 9-12 months.

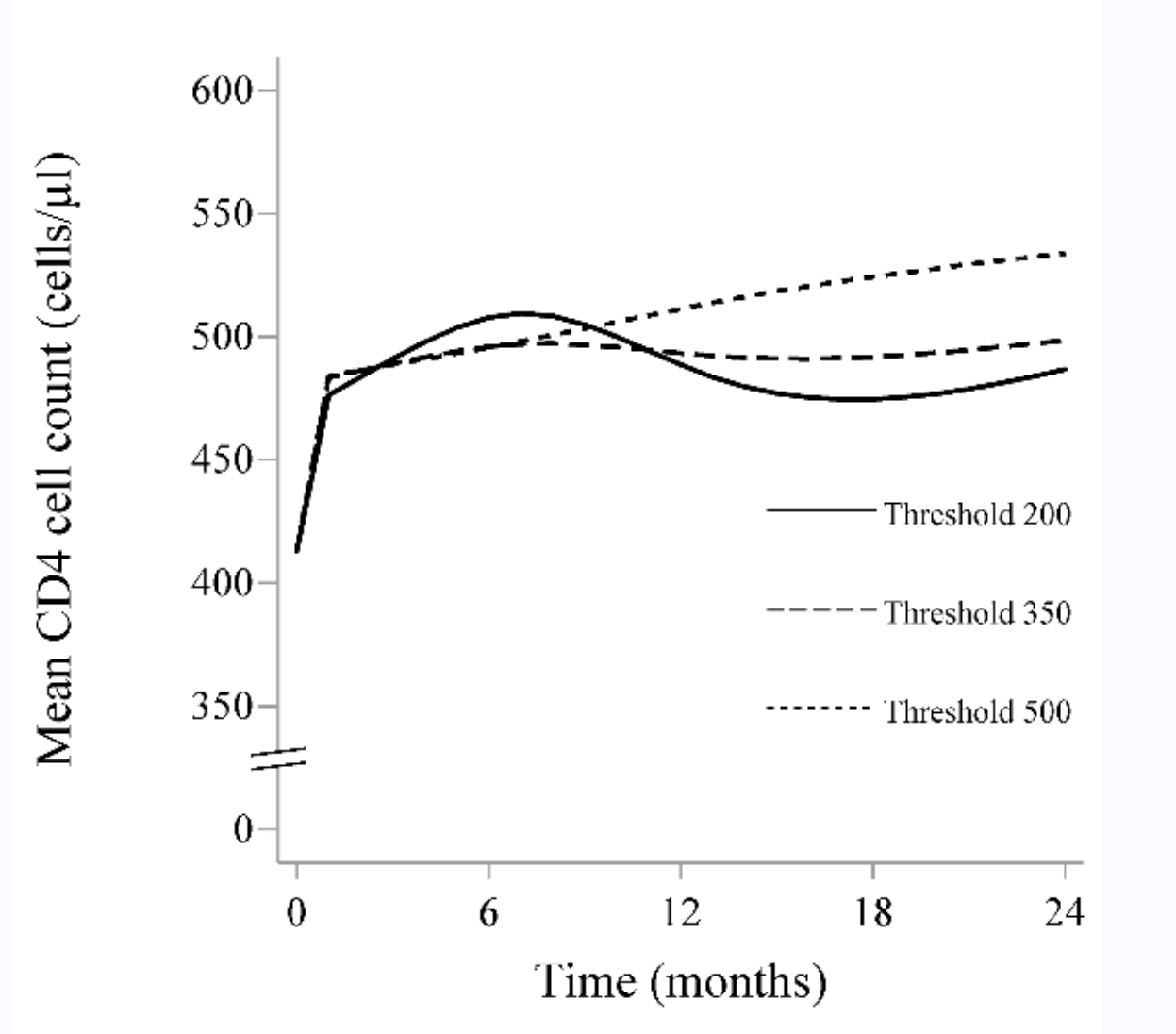


Appendix Figure 2. 24-month mean CD4 cell curves by monitoring strategy, CNICS and HIV-CAUSAL Collaboration 2000-2015



The curve is standardized by the baseline covariates: sex, CD4 cell count (≤200, 201-350, 351-500, ≥501 cells/µl), years since HIV diagnosis (<1, 1-4, ≥5 years, unknown), race (white, black, other or unknown), geographic origin (N. America/W. Europe, Sub-Saharan Africa, other, unknown), acquisition group (heterosexual, homosexual or bisexual, injection drug use, other or unknown), calendar year (restricted cubic splines with 3 knots at 2001, 2007 and 2011), age (restricted cubic splines with 3 knots at 25, 39 and 60 years), cohort, and months from cART initiation to virologic suppression (2-4, 5-8, ≥9). We adjusted for potential selection bias induced by artifical censoring using inverse probability weighting.

Appendix Figure 3. 24-month mean CD4 cell curves by monitoring strategy adjusting for baseline confounding only, CNICS and HIV-CAUSAL Collaboration 2000-2015



The curve is standardized by the baseline covariates.

References

1. Cain LE, Saag MS, Petersen M, et al. Using observational data to emulate a randomized trial of dynamic treatment-switching strategies: an application to antiretroviral therapy. *International journal of epidemiology* 2015.